

EXHIBIT

3-5

FUNGAL IMMUNOMODULATORY PROTEIN (FIP) PREPARED BY

MICROORGANISMS AND USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The invention relates to an improved nucleic acid molecule encoding fungal immunomodulatory protein (FIP) that is better expressed in fungi, to vectors comprising the nucleic acid molecule, to hosts transformed with said vectors, to processes of expressing the protein of the invention in said transformed hosts, to the protein of the invention produced by said processes, to uses of said hosts comprising the protein of the invention and to a process of purifying FIP. The protein of the invention has wide immunomodulatory activity. Thus, the present invention further relates to uses of the protein of the invention in cosmetic or pharmaceutical compositions and to food or feed additives comprising the protein of the invention. Finally, the invention relates to the method of modulating immunological activities by orally administering FIP or proteins fused with FIP to a subject.

Description of the Prior Art

[0002] Lectins from Fungal fruit bodies or mycelia have immunomodulatory and hepatoprotective effects that have been suggested to be able to remove free radicals (Lin J.M. et al., *Am J Chin Med.* 1993;21(1):59-69). (L)-galactoside-specific lectins from mistletoe enhance cytokine production *in vitro* and *in vivo* (Gabijs H.J. et al., *Anticancer Res.* 1992 May-Jun;12(3):669-75). In a test using Balb/C mouse as the disease model, lectins and recombinant lectins can inhibit tumor formation (Couraud P.O. et al., *J. Biol. Chem.* 1989; 264:1310-1316).

[0003] Ganoderma is a rare and valuable herb in Chinese medicine. It has been known in China for over 5,000 years as "Ling Zhi". There are a variety of ganodenmas, including *G. lucidum* (red), *G. applanatum* (brown), *G. tsugae* (red), *G. sinense* (black), and *G. oregonense* (dark brown).

[0004] Several proteins from edible fungi such as *Ganoderma Lucidium* (Ling zhi or Reishi), *Volvariella Volvacea* (Chinese Mushroom), *Flammulina Velutipes* (Golden needle mushroom) share similar amino acid sequences and immunomodulatory functions. These proteins were named fungal immunomodulatory proteins (FIPs) (Ko J.L., *Eur. J. Biochem.* 1995; 228:224-249). Among all health foods in Chinese medicine, Ling Zhi is the best-studied fungus.

[0005] It has been known that Ling Zhi has anti-allergy (Chen H.Y et al., *J. Med. Mycol.* 1992; 33:505-512), hepatoprotective (Lin J.M. et al., *Am J Chin Med.* 1993;21(1):59-69), anti-tumor effects (Wasser SP(1999), *Crit Rev*